| FORM PTO-1390 (REV 11-98) | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | ATTORNEY'S DOCKET NUMBER 888-50 |
|---|---|---|

**TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371**

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): 09/762630 Unknown

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/IB99/01460 | 12 August 1999 | 12 August 1998 |

TITLE OF INVENTION

**NIMESULIDE CONTAINING TOPICAL PHARMACEUTICAL COMPOSITIONS**

APPLICANT(S) FOR DO/EO/US

**EMBIL et al.** EMBIL KORAL

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☒ has been transmitted by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☐ have been transmitted by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
   - d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. To 16. Below concern document(s) or information included:**

11. ☐ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information. **PTO-1449/ International Search Report**
    ☐ This application is entitled to "Small entity" status. ☐ "Small entity" statement attached.

| U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) | INTERNATIONAL APPLICATION NO | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 09/926630 Unknown | PCT/IB99/01460 | 888-50 |

17. ☒ The following fees are submitted:

| | CALCULATIONS | PTO USE ONLY |
|---|---|---|
| **BASIC NATIONAL FEE (37 C.F.R. 1.492(a)(1)-(5):** | | |
| -- Neither international preliminary examination fee (37 C.F.R. 1.482) nor international search fee (37 C.F.R. 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... $1000.00 | | |
| -- International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... $860.00 | | |
| -- International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but international search fee (37 C.F.R. 1.445(a)(2) paid to USPTO ..... $710.00 | | |
| -- International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... $690.00 | | |
| -- International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... $100.00 | | |
| **ENTER APPROPRIATE BASIC FEE AMOUNT =** | $ 860.00 | |
| Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 C.F.R. 1.492(e)). | $ 130.00 | |

| CLAIMS | NUMBER FILED | | NUMBER EXTRA | RATE | | | |
|---|---|---|---|---|---|---|---|
| Total Claims | 18 | -20 = | 0 | X | $18.00 | $ | 0.00 |
| Independent Claims | 3 | -3 = | 0 | X | $80.00 | | 0.00 |
| MULTIPLE DEPENDENT CLAIMS(S) (if applicable) | | | | | $270.00 | $ | 0.00 |
| **TOTAL OF ABOVE CALCULATIONS =** | | | | | | $ | **990.00** |
| Reduction by ½ for filing by small entity, if applicable. Small entity status must also be asserted. (Note 37 C.F.R. 1.9, 1.27, 1.28). | | | | | | | 0.00 |
| **SUBTOTAL =** | | | | | | $ | **990.00** |
| Processing fee of $130.00, for furnishing the English Translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. 1.492(f)). + | | | | | | | 0.00 |
| **TOTAL NATIONAL FEE =** | | | | | | $ | **990.00** |
| Fee for recording the enclosed assignment (37 C.F.R. 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). **$40.00** per property + | | | | | | $ | 0.00 |
| Fee for Petition to Revive Unintentionally Abandoned Application ($1240.00 – Small Entity = $620.00) | | | | | | $ | 0.00 |
| **TOTAL FEES ENCLOSED =** | | | | | | $ | **990.00** |
| | | | | | | Amount to be: refunded | $ |
| | | | | | | Charged | $ |

a. ☒ A check in the amount of $990.00 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 14-1140 in the amount of $_____ to cover the above fees. A duplicate copy of this form is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1140. A duplicate copy of this form is enclosed.
d. ☐ The entire content of the foreign application(s), referred to in this application is/are hereby incorporated by reference in this application.

**NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

**SEND ALL CORRESPONDENCE TO:**

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SIGNATURE

**James T. Hosmer**
NAME

**30,184** REGISTRATION NUMBER

**February 12, 2001** Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

EMBIL et al.

Atty. Ref.: 888-50

Serial No. Unknown

Group:

Filed: February 12, 2001

Examiner:

For: NIMESULIDE CONTAINING TOPICAL PHARMACEUTICAL COMPOSITIONS

Assistant Commissioner for Patents
Washington, DC 20231
Sir:

February 12, 2001

**PRELIMINARY AMENDMENT**

In order to place the above-identified application in better condition for examination, please amend the application as follows:

**IN THE CLAIMS**

Claim 5, line 1, delete "or 4".
Claim 6, line 1, delete "or 4".
Claim 7, line 1, change "any of claims 3 to 6" to --claim 3--.
Claim 9, line 1, change "any of claims 3 to 8" to --claim 3--.
Claim 11, line 1, delete "or 10".
Claim 12, line 1, change "any of claims 3 to 11" to --claim 3--.
Claim 14, line 1, change "any preceding claims" to --claim 1--.
Claim 15, line 1, change "any preceding claims" to --claim 1--.
Claim 16, line 1, change "any preceding claims" to --claim 1--.
Claim 17, line 1, delete "or 16".
Claim 18, line 1, change "any of claims 15 to 17" to --claim 15--.

**REMARKS**

The above amendments are made to place the claims in a more traditional format.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: _____
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# NIMESULIDE CONTAINING TOPICAL PHARMACEUTICAL COMPOSITIONS

This invention relates to compositions of nimesulide for topical application.

Nimesulide is a nonsteroidal anti-inflammatory agent (NSAID), which has poor solubility, especially in water. It has been formulated at various concentrations as a suspension in vehicles containing pharmaceutically acceptable excipients. These vehicles typically consist of aqueous gels containing about 1% nimesulide. Nimesulide in suspension may have limited therapeutic activity, as its percutaneous absorption is impaired by the difficulty of releasing free drug molecules from the suspensoid. Solubilised nimesulide, on the other hand, may offer the advantage of immediate availability of free drug molecules to the receptor site, and gels comprising solubilised nimesulide have been prepared using different pharmaceutical solvents. However, when the gel products comprising solubilised nimesulide are applied topically, they produce an unpleasant yellowish stain on the skin and/or clothing.

Many attempts have been made to provide nimesulide compositions of various kinds. They include those described in EP-A-0782855 and EP-A-0812587. In EP-A-0782855, particles of nimesulide are dispersed (not dissolved) in a base component. In EP-A-0812587, nimesulide is incorporated in a medium vaguely described as a "percutaneous absorption enhancing vehicle base", which comprises water as an essential ingredient and a surfactant such as glyceryl monoolein in an amount of up to 12% w/w.

Accordingly, it is an objective of the present invention to provide nimesulide compositions, which are both therapeutically effective and non-staining or substantially non-staining when applied topically. It has been found that this desirable combination of properties is achieved in the compositions of the present invention. The compositions of the present invention may enable the nimesulide to penetrate the upper layer of the skin (stratum corneum) rapidly. Once within the stratum corneum, the nimesulide may be released into the deeper layers of the skin more slowly, which is advantageous in the treatment of the conditions for which nimesulide is used.

The invention provides a composition for topical application comprising nimesulide in a glyceryl monoolein-solvent phase comprising glyceryl monoolein in an amount of 17-59% by weight of the composition.

The invention further provides a composition for topical application comprising nimesulide in a glyceryl monoolein-solvent phase, wherein the glyceryl monoolein-solvent phase may have a liquid crystal structure.

The invention further provides a composition for topical application comprising nimesulide, glyceryl monoolein and a non-aqueous solvent. Optionally the composition may also comprise a gelling agent, water and other additives.

The nimesulide is preferably used in the composition in an amount of 0.1-5% by weight, more preferably in an amount of 0.1-3% by weight, most preferably in an amount of around 1% by weight of the composition.

The glyceryl monoolein (or monooleate) may be used in an amount as low as 10-45% by weight, preferably in an amount of 17-45% by weight, more preferably in an amount of 17-59% by weight of the composition. Glyceryl monoolein is available commercially as a distilled monoglyceride mixture with a high monoolein content (for example "GMOrphic" from Eastman Chemicals, USA, or "Glycerol Monooleate" from an alternative manufacturer).

The non-aqueous solvent is preferably used in an amount of 40-82% by weight, more preferably 60-82% by weight of the composition. The solvent should be pharmaceutically acceptable and may for example be a $C_{1-6}$ alcohol, N-methylpyrrolidone, a glycol or an ether glycol (e.g. a $C_{2-6}$ compound such as propylene glycol, 1,3-butylene glycol, dipropylene glycol or diethylene glycol), an ether (e.g. a $C_{2-6}$ ether such as diethyl ether or diethylene glycol monoethyl ether (DGME)), or a $C_{8-22}$ glyceride or ethoxylated glyceride (e.g. capric, caprylic, arachinoic and behanoic glycerides and ethoxylated derivatives thereof, particularly caprylic/capric triglycerides or derivatives containing for example 6 polyoxyethylene units). Mixtures of these solvents can also be used. Preferably a solvent system containing DGME and a $C_{1-6}$ alcohol such as ethanol is used, preferably

with the DGME in an amount of 35-45% by weight and the alcohol in an amount of 25-35% by weight of the composition. More preferably DGME is used on its own as solvent, preferably in an amount of 40-82% by weight, more preferably in an amount of 60-82% by weight of the composition.

The composition may also optionally include a gelling agent such as hydroxypropylcellulose or a fumed silicon dioxide (e.g. Cab-O-Sil). Preferably hydroxypropylcellulose is used. Although gelling agents are not required, they may assist in maintaining the long-term structural integrity and can influence the shelf life stability of a finished product. Gelling agents can additionally offer greater flexibility to the formulator in designing finished products with varied consistence and levels of thickness. Preferably gelling agents are used in an amount of 0.1-10% by weight, more preferably in an amount of 0.5-3% by weight of the composition.

The composition need not contain any water. However, it may optionally include water, preferably in amount of up to 15% by weight (for example 5-15% by weight), more preferably in an amount of up to 10% by weight of the composition.

Other ingredients may also optionally be included in the composition, for example capsicum oleoresin, capsaicin, nicotinates, camphor, menthol, turpentine oil, preservatives (e.g. propylparaben), antioxidants (e.g. BHT or BHA), sequestrant agents (e.g. EDTA) or colorants (e.g. FD&C Blue 1 or Yellow #5). Preferably such optional additives are included in an amount of up to 0.25% by weight, for example 0.001-0.25% by weight of the composition.

Preferably, the composition is in the form of a gel, solution, ointment or spray. Most preferably the composition is in the form of a gel. A gel is easy to apply – it does not drip like a solution may, and the dosage of a gel is usually more easily controlled than that of a spray. The gel may be a jelly-like material, for example formed from a nimesulide solution by the addition of a gelling agent. A nimesulide spray may be a nimesulide solution in a spraying device.

The nimesulide compositions can be used for a variety of indications characterised by pain and inflammation, or stiffness. Such indications are: osteoarthritis of superficial joints, such as the knee, ankle, wrist and elbow; rheumatism; acute musculoskeletal injuries and/or bruising; muscular cramp; strains; sprains; periarthritis; epicondylitis; tendinitis; bursitis; tenosynovitis; tennis elbow; back strain; lumbago; sciatica; neuralgia; and fibrositis.

The compositions may be prepared by first dissolving the nimesulide in the non-aqueous solvent(s) to form a solution. This solution may be heated to 30-90°C and mixed with glyceryl monoolein, which may have previously been heated to 35-55°C. This mixing step may be followed by agitation and cooling to room temperature to form a clear nimesulide solution.

This clear nimesulide solution may alternatively be prepared by first dissolving glyceryl monoolein in the non-aqueous solvent(s) to form a solution. This solution may be heated to 30-90°C and mixed with nimesulide, followed by agitation and cooling to room temperature to form a clear nimesulide solution.

Optionally, a gelling agent may be mixed into the nimesulide solution, either on its own or as a gel prepared with the non-aqueous solvent(s). If water and other optional additives are included in the composition, these may be mixed into the composition as a final step.

The present invention makes it possible to provide compositions, which have the advantage that they do not leave yellow stains on the skin and clothing upon application. It is believed that the nimesulide compositions of the present invention may be in the form of a liquid crystal structure.

The compositions are applied topically to the skin, which should be clean and is preferably cleansed before use. Cleaning provides a better surface for penetration by the composition, thus assisting in avoiding staining, and prevents surface materials such as salt or grime from complexing with any gelling agent present and coagulating the composition.

The following examples illustrate the invention.

Example 1

| | |
|---|---|
| Diethylene glycol monoethyl ether (DGME) | 42.5% w/w |
| SD alcohol (ethanol) | 30% w/w |
| Water | 10% w/w |
| Nimesulide | 1% w/w |
| Glyceryl monoolein | 16.5% w/w |

The nimesulide was dissolved in DGME and ethanol to form a solution, which was heated to 45°C. This heated solution was added to glyceryl monoolein, which had previously been heated to 45°C. The mixture was agitated and cooled to room temperature to give a clear solution, to which water was added.

Example 2

| | |
|---|---|
| Diethylene glycol monoethyl ether (DGME) | 40% w/w |
| SD alcohol (ethanol) | 25.5% w/w |
| Water | 10% w/w |
| Fumed silicon dioxide | 7% w/w |
| Nimesulide | 1% w/w |
| Glyceryl monoolein | 16.5% w/w |

The nimesulide was dissolved in DGME and ethanol to form a solution, which was heated to 45°C. This heated solution was added to glyceryl monoolein, which had previously been heated to 45°C. The mixture was agitated and cooled to room temperature to give a clear solution. The gelling agent (silicon dioxide) was then mixed into the solution to the desired consistency to provide a clear gel. Finally water was mixed into the gel.

Alternatively, the nimesulide was added slowly to DGME at 48-50°C to form a solution. Glyceryl monoolein was heated to 48-50°C and added slowly to the nimesulide solution with mixing to give a clear nimesulide solution, which was cooled to room temperature. Ethanol and gelling agent were mixed thoroughly to form an alcoholic gel,

which was mixed slowly into the nimesulide solution at room temperature to give a clear gel. Finally water was mixed into the gel.

Example 3

| | |
|---|---|
| Diethylene glycol monoethyl ether (DGME) | 42.5% w/w |
| SD alcohol | 30% w/w |
| Water | 10% w/w |
| Nimesulide | 1% w/w |
| Glyceryl monoolein | 16.475% w/w |
| Capsaicin | 0.025% w/w |

A clear gel was prepared as described in Example 1. The capsaicin was then added in a final step and mixed into the gel until dissolved and homogenous.

Example 4

| | |
|---|---|
| Diethylene glycol monoethyl ether (DGME) | 81% w/w |
| Hydroxypropylcellulose | 1% w/w |
| Nimesulide | 1% w/w |
| Glyceryl monoolein | 17% w/w |

The nimesulide was dissolved in DGME to form a clear solution, which was heated to 43-47°C. Glyceryl monoolein was heated to 43-47°C and mixed into the solution to form a clear solution, which was mixed and cooled to room temperature. The mixing speed was increased enough to create a vortex of mixing, and hydroxypropylcellulose was added. The mixing was continued until a clear gel was obtained.

Example 5

| | |
|---|---|
| Diethylene glycol monoethyl ether (DGME) | 63.1% w/w |
| Hydroxypropylcellulose | 1.4% w/w |
| Nimesulide | 1% w/w |
| Glyceryl monoolein | 34.5% w/w |

A gel was obtained using the method described in Example 5.

| Example 6 | |
|---|---|
| Diethylene glycol monoethyl ether (DGME) | 82% w/w |
| Nimesulide | 1% w/w |
| Glyceryl monoolein | 17% w/w |

The nimesulide was dissolved in DGME to form a clear solution, which was heated to 43-47°C. Glyceryl monoolein was heated to 43-47°C and mixed into the solution to form a clear solution, which was mixed and cooled to room temperature.

Upon visual inspection, a clear transparent medium was observed and no nimesulide crystals were observed, suggesting that the nimesulide was only present in solution. The compositions of the Examples were also found to be physically stable, for example it was possible to keep them at 40°C for 60 days or more.

Claims

1. A composition comprising nimesulide in a glyceryl monoolein-solvent phase comprising glyceryl monoolein in an amount of 17-59% by weight of the composition.

2. A composition comprising nimesulide in a glyceryl monoolein-solvent phase, wherein the glyceryl monoolein-solvent phase has a liquid crystal structure.

3. A composition comprising nimesulide in an amount of 0.1-5% by weight of the composition, glyceryl monooleate in an amount of 17-59% by weight of the composition and a non-aqueous solvent in an amount of 40-82% by weight of the composition.

4. A composition according to claim 3, wherein the nimesulide is used in an amount of 0.1-3% by weight, preferably in an amount of about 1% by weight of the composition.

5. A composition according to claim 3 or 4, wherein the non-aqueous solvent is a solvent system containing DGME in an amount of 35-45% by weight and ethanol in an amount of 25-35% by weight of the composition.

6. A composition according to any of claims 3 or 4, wherein the non-aqueous solvent is DGME used in an amount of 40-82% by weight, preferably in an amount of 60-82% by weight of the composition.

7. A composition according to any of claims 3 to 6, which further comprises a gelling agent in an amount of 0.5-3% by weight of the composition.

8. A composition according to claim 7, wherein the gelling agent is hydroxypropylcellulose.

9. A composition according to any of claims 3 to 8, which further comprises water in an amount of 0-15% by weight of the composition.

10. A composition according to claim 9, wherein water is used in an amount of 0-10% by weight of the composition.

11. A composition according to claim 9 or 10, wherein the composition does not contain any water.

12. A composition according to any of claims 3 to 11, which further comprises at least one other additive in an amount of up to 0.25% by weight, preferably 0.001-0.25% by weight of the composition.

13. A composition according to claim 12, wherein the at least one other additive is selected from the group consisting of capsicum oleoresin, capsaicin, nicotinates, camphor, menthol, turpentine oil, preservatives such as propylparaben, antioxidants such as BHT or BHA, sequestrant agents such as EDTA or colorants such as FD&C Blue 1 or Yellow #5.

14. A composition according to any preceding claims, wherein the composition is in the form of a gel, solution, ointment or spray; preferably a gel.

15. A process for the preparation of a composition according to any preceding claims, which comprises the following steps:

(i) dissolving nimesulide in non-aqueous solvent(s) to form a solution, which is heated to 30-90°C;

(ii) mixing this solution with glyceryl monoolein, which has previously been heated to 35-55°C;

(iii) followed by agitation and cooling to room temperature to form a clear nimesulide solution.

16. A process for the preparation of a composition according to any preceding claims, which comprises the following steps:

(i) dissolving glyceryl monoolein in non-aqueous solvent(s) to form a solution, which is heated to 30-90°C;

(ii) mixing this solution with nimesulide;

(iii) followed by agitation and cooling to room temperature to form a clear nimesulide solution.

17. The process of claim 15 or 16, further comprising the step of:

(iv) mixing a gelling agent into the nimesulide solution, either on its own or as a gel prepared with the non-aqueous solvent(s).

18. The process of any of claims 15 to 17, further comprising the step of:

(v) mixing water into the solution or gel.

**RULE 63 (37 C.F.R. 1.63)**
**INVENTORS DECLARATION FOR PATENT APPLICATION**
**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

As a below named inventor, I hereby declare that my residence, mailing address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NIMESULIDE CONTAINING TOPICAL PHARMACEUTICAL COMPOSITIONS

the specification of which (**check** applicable **box(s)**):

☐ is attached hereto
☒ was filed on February 12, 2001 as U.S. Application Serial No. 09/762,630 (Atty Dkt. No. 888-50)
☒ was filed as PCT International application No. PCT/IB99/01460 on 12 August 1999
and (if applicable to U.S. or PCT application) was amended on

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose to the Patent Office all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application:

Priority Foreign Application(s):

| Application Number | Country | Day/Month/Year Filed |
|---|---|---|

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

| Application Number | Date/Month/Year Filed |
|---|---|

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below:

| Prior U.S./PCT Application(s): Application Serial No. | Day/Month/Year Filed | Status: patented pending, abandoned |
|---|---|---|
| PCT/IB99/01460 | 12 August 1999 | |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. And on behalf of the owner(s) hereof, I hereby appoint **NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8th Floor, Arlington, VA 22201-4714, telephone number (703) 816-4000 (to whom all communications are to be directed)**, and the following attorneys thereof (of the same address) individually and collectively owner's/owners' attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Larry S. Nixon, 25640; Arthur R. Crawford, 25327; James T. Hosmer, 30184; Robert W. Faris, 31352; Richard G. Besha, 22770; Mark E. Nusbaum, 32348; Michael J. Keenan, 32106; Bryan H. Davidson, 30251; Stanley C. Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Jeffry H. Nelson, 30481; John R. Lastova, 33149; H. Warren Burnam, Jr. 29366; Mary J. Wilson, 32955; J. Scott Davidson, 33489; Alan M. Kagen, 36178; Robert A. Molan, 29834; B. J. Sadoff, 36663; James D. Berquist, 34776; Updeep S. Gill, 37334; Michael J. Shea, 34725; Donald L. Jackson, 41090; Michelle N. Lester, 32331; Frank P. Presta, 19828; Joseph S. Presta, 35329; Joseph A. Rhoa, 37515; Raymond Y. Mah, 41426; Chris Comuntzis, 31097. I also authorize Nixon & Vanderhye to delete any attorney names/numbers no longer with the firm and to act and rely solely on instructions directly communicated from the person, assignee, attorney, firm, or other organization sending instructions to Nixon & Vanderhye on behalf of the owner(s).

1-00

1. Inventor's Signature: _____ Date: _____
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Mailing Address: c/o Embil Pharmaceutical Company Limited, P. O. Box 226, Sisli, Istanbul, Turkey
(Zip Code) 80223

2-00

2. Inventor's Signature: _____ Date: 3/26/01
Inventor: Ray (first) MI FIGUEROA (last) United States (citizenship)
Residence: (city) Medley (state/country) Florida
Mailing Address: c/o R.F. Technology Consultants, Inc. 8242 N.W South River Drive, Medley, Florida
(Zip Code) 33166

☐ *See attached sheet(s) for additional inventor(s) information!!*